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09/149,718	09/08/1998	KATE DORA GAMES	ANS-101-CIP(	5407

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EXAMINER
CROUCH, DEBORAH

ART UNIT	PAPER NUMBER
1632	22

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/149,718	Applicant(s) GAMES ET AL.	
	Examiner Deborah Crouch	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,22-26,29-55,57 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,22-26,29-55,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The request filed on January 31, 2002 in paper no. 21 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/149,718 is acceptable and a CPA has been established. An action on the CPA follows.

Applicant's arguments filed August 2, 2001 in paper no. 16 have been fully considered but they are not fully persuasive. The amendment has been entered. Claims 1-20,22-26,29-55,57 and 58 are pending. The formal drawings, and corrections, filed January 29, 2001 have been approved by the draftsman.

Applicant's amendment has over come the rejection of claims 1-20,22,23,26,29-50,53,54,57 and 58 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,811,633 claims 1-6 of U.S. Patent No. 5,720,936. Applicant has specifically disclaimed subject matter encompassing the claimed subject matter in '633 and 936.

Applicant's amendment and arguments that they have specifically disclaimed subject matter the encompasses the claims in U.S. Patent 5,811,633 and U.S. Patent 5,720,936 nullifies the previously stated request under 37 CFR 1.78(c) and 35 U.S.C. 132.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20,22-26,29-55,57 and 58 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7,9-16 and 18-27 of copending Application No. 09/149,856 for reasons of record as set forth in papers no. 5, mailed April 27, 2000 and no. 11, mailed January 29, 2001. Although the

conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and '856 are obvious over each other.

This is a provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Applicant reiterates that they will consider filing a terminal disclaimer once allowable subject matter has been indicated.

Claims 1,2,5-20,24-26,28-30,33-48,51-53 and 56-58 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,612,486 for reasons of record as set forth in papers no. 5, mailed April 27, 2000 and no. 11, mailed January 29, 2001. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and '486 are obvious over each other.

Claims 1,2,5-20,24-26,28-30,33-48,51-53 and 56-58 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6 and 10-12 of U.S. Patent No. 5,604,102 for reasons of record as set forth in papers no. 5, mailed April 27, 2000 and no. 11, mailed January 29, 2001. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Applicant refers to their arguments regarding the prior art rejection over each of '486 and '102 below. The examiner will defer any rebuttal until the prior art arguments are reached.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1,2,5-7,9,11,13,15-20,24-26,29-30,33,34,36,38,40,42-48,51-53,57 and 58 remain rejected under 35 U.S.C. 102(a) as being clearly anticipated by WO 95/11968 for reasons of record as set forth in papers no. 5, mailed April 27, 2000 and no. 11, mailed January 29, 2001.

'968 teaches a method for identifying drugs effective in the treatment of Alzheimer's Disease wherein the assay comprising administering drugs of interest to transgenic non-human mammals that express the Swedish mutation APP operatively linked to the rat NSE promoter (page 39-40, bridg. parag.; page 41, lines 16-22 and page 42, lines 17-24). As the construct disclosed in '986 is also claimed by applicant, the expression levels, characteristics and features claimed for the mouse of the instant assay are an inherent feature of the mouse of the assay in '968.

Applicant argues that the ordinary artisan attempting to produce transgenic mice in accordance with the teaching of WO 95/11968 would not necessarily have obtained a transgenic animal having the expression levels of Aβ peptide recited in the present claims. Applicant argues that expression levels resulting from any particular transgenic expression may depend not only on the nature of the transgene, but also on unpredictable factors such as the chromosomal location at which the transgene integrates and the numbers of copies of the transgene that integrate per genome. Applicant argues that although the transgenic animals produced according to WO 95/11968 have transgenes that fall within the present claims, they do not have other structural requirements such as appropriate chromosomal location and copy number to achieve the expression levels of Aβ peptide recited in the present claims.

Applicant argues that whether or not the artisan would have achieved a transgenic animal have the expression levels of Aβ peptide recited depends on many variables. Applicant argues

that these variables include that the number of animals that the artisan would be prepared to screen, the criteria that the artisan used in screening and the probability that a given transgenic animal produced in accordance with the teachings of the cited reference would have the recited expression levels of Aβ peptide. Applicant argues that a researcher screening by a different criterion would not necessarily obtain a transgenic animal with the recited expression levels of Aβ peptide. Applicant argues that the cited reference provides no indication of the frequency with which the a transgene described in the reference might integrate so as to give rise to expression levels of Aβ peptide recited in the claims. Applicant sums the arguments in stating that whether the artisan would have achieved a transgenic animal having the expression levels of Aβ peptide recited in the present claims would have been a matter of subject factors, probabilities and unknowns. These arguments are not persuasive.

The rejection is the that claimed method of testing compounds for an effect on an Alzheimer's Disease marker using a transgenic mouse encompass methods of assay disclosed in WO 95/1411968. That is to say, that when the structural features of the transgene, that is the promoter or expression regulatory sequences and the DNA sequence encoding APP, that was used in the production of the mouse, are compared to the transgene of the mouse used in the presently claimed assays, the transgene of '968 is embodied in the present claims. Thus, the mouse of '968 has the same structure as an embodiment of the present claims. If a claimed product, and the transgenic mouse is a product, has the same structure or embodies the same structure of a transgenic mouse in the art, then both mice will have the same phenotype or phenotypes. It is not relevant to patentability that the mouse of the prior art ever be shown to have the presently claimed phenotype. If the transgenic mouse of '698 has the same promoter and the same DNA sequence, then that mouse will reach the claimed expression levels. The art

nor the artisan never have to demonstrate such. The burden is shifted to applicant to demonstrate that the mouse '968 never expresses at the claimed levels, nor develops any claimed phenotype. Whether or not the artisan spends much time, a lot of time or no time, uses any particular assay, if the structure is the same the expectation is that the phenotypes are the same whether or not the phenotypes are ever recognized.

Applicant argues *Mel/Biophile v. Milgraum,* which states that inherency may not be established by probabilities or possibilities; *In re Rijakaert,* which states that the mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency. Applicant argues that the examiner must show that invariably those animals having the construct of '968 will exhibit the claimed phenotypes. Applicant further argues *Gubelmann v Gang*, which states that it is not sufficient that a person following the disclosure might obtain the result set forth in the count, it must invariably happen, and *In re Oelrich*, when a references is silent about the asserted inherent characteristic ... evidence must make clear that the missing descriptive matter is necessarily present in the thing described". These arguments are not persuasive.

Applicant has not provided any evidence that the mice of '968 will not exhibit the claimed expression levels. The probability that applicant argues is that the artisan may not know the phenotype because the artisan may not assay a sufficient number of mice, or may use the wrong assay criteria. This does not rise to the level that the mice will not have the phenotype. A phenotype is not required to be recognized or known to be inherent. If the structure of the transgene of the transgenic mice is the same, or is an embodiment of applicant's claim it will be expressed to the recited expression level. Why wouldn't it? Copy number isn't the answer. The mice in '968 did express the APP transgene. Why wouldn't the mice of '968 if assayed under applicant's conditions express at this level? There is no possibility that the transgene won't be so

expressed. Applicant's claims states that the transgene is expressed to a particular level. Applicant needs to supply evidence that the mice of '968 do not show the phenotype.

Applicant argues that those of ordinary skill in the art must recognize and appreciate the allegedly inherent feature (*In re Oelrich* and *Glaxo v. Novopharm)*. This argument is not persuasive.

Applicant has not explained why the ordinary artisan would not recognize or appreciate the fact that the mice of '968 contain a transgene encompassed by the claims, and that the transgene, since it is structurally indistinguishable from an embodiment of applicant's, would be expected to express the transgene to the same level as that claimed by applicant.

Further, the case law clear states:

"When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997).

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433. See the M.P.E.P. 2112.01

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7,9,11,13,15-20,22,23,26,29-34,36,38,40,42-50,53,54,57 and 58 remain rejected under 35 U.S.C. 102(b) as being clearly anticipated by WO 93/14200 for reasons of record as set forth in papers no. 5, mailed April 27, 2000 and no. 11, mailed January 29, 2001.

'200 teaches a method of screening for compounds effective in the treatment of Alzheimer's Disease wherein the treatment assay comprises transgenic mice or transformed cells that express a transgene encoding APP770, APP751, APP695, APP770 with FAD mutations at amino acid 717 operably linked to the PDGFβ promoter (page 14, parag. 1, page 15, parag. 1, page 16, parag. 1, pages 18, parag. 1, lines 4-5 and pages 28-30). The construct disclosed in '200 is the same as that claimed by applicant, and as such the expression levels, characteristics and features of the mouse of the assay claimed by applicant are an inherent feature of the mouse testing model disclosed in '200.

Applicant argues that the amendment to the claims renders the rejection moot. This argument is not persuasive.

The amendment only excludes a particular cDNA/genomic APP construct comprising an APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6,7, and

8, and exons 7 and 8. '200, however, teaches the use of any APP cDNA/genomic hybrid construct ('200, page 9, lines 14-16). Thus, '200 teaches the assays using mice comprising transgene constructs within the scope of the claims. In particular see present claim 3. Thus, while applicant has excluded one disclosed, and claimed, APP cDNA/genomic DNA construct, '200 teaches non-excluded APP cDNA/genomic DNA construct.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1,7,9,11,13,15-20,22,23,26,29-34,36,38,40,42-50 and 53-58 remain rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S. Patent No. 5,720,936 issued February 24, 1998 for reasons of record as set forth in papers no. 5, mailed April 27, 2000 and no. 11, mailed January 29, 2001.

'936 teaches the an assay system comprising transgenic mice whose genome comprises and expresses a variety of APP transgene constructs: cDNA encoding APP770, APP751, APP695 and FAD mutants of these cDNA's and a cDNA genomic construct, a specific version of which is claimed (col. 8, 13-22, lines 46 to col. 9, line 23; and claims 1-6). The construct is disclosed and claimed to be operatively linked to a promoter, and such as the PDGF promoter (col. 9, lines 60-64 and claims 1,3 and 4).

Applicant argues that the amendment to the claims renders the rejection moot. This argument is not persuasive.

The amendment only excludes a particular cDNA/genomic APP construct comprising an APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6,7, and 8, and exons 7 and 8. '936, however, teaches the use of any APP cDNA/genomic hybrid construct ('936, col. 5, lines 21-25). Thus, '936 teaches the assays using mice comprising transgene

constructs within the scope of the claims. In particular see present claim 3. Thus, while applicant has excluded one disclosed, and claimed, APP cDNA/genomic DNA construct, '936 teaches non-excluded APP cDNA/genomic DNA construct.

Claims 1,2,5-7,9,11,13,15-20,24-26,29,33,34,36,37,39,40,42-45,51-53,57 and 58 remain rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S. Patent No. 5,604,102 issued February 18, 1997 for reasons of record as set forth in papers no. 5, mailed April 27, 2000 and no. 11, mailed January 29, 2001.

'102 teaches a method of assay employing a transgenic mouse whose genome comprises a transgene comprising APP695 K595M, N596L, the Swedish mutation operably linked to the NSE promoter (col. 15, lines 26-31 and col. 20, lines 16-20, and claims 1-16). These mutations are identical to K670M, N671L.

Applicant states that '102 and WO 95/11968 are similar in disclosure, and the rejection of claims over '102 raises the same issues as does the rejection over '968. Applicant refers to those arguments.

Similarly, the examiner refers applicant to the rebuttal of arguments against the rejection over '968.

(f) he did not himself invent the subject matter sought to be patented.

Applicant's amendments claims 1-7,9,11,13,15-20,22,23,26,28-34,36,38,40,42-50 and 53-58 remain rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter for reasons of record as set forth in papers no. 5, mailed April 27, 2000 and no. 11, mailed January 29, 2001.

'936 is presently commonly assigned to Athena Neurosciences. The record indicates that at the time of invention '936 was assigned to TSI Corporation in paper no. 3 filed August 31, 1992.

Applicant argues that the citation of the '936 patent under 35 35 USC § § 102(f) as under 102(e). Applicant states that they respond the same.

Applicant is referred to the rebuttal of the rejection under 35 35 USC § § 102(e) over U.S. Patent 5,720,936.

Claims 1,2,5-7,9,11,13,15-20,24-26,29,33,34,36,38,40,42-45,51-53 and 56-58 remain rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter for reasons of record as set forth in papers no. 5, mailed April 27, 2000 and no. 11, mailed January 29, 2001.

Applicant argues the citation of U.S. Patent 5,602,102 under 102(f) raises the same issues as the rejection under 102(e) and that they respond the same.

The examiner refers applicant's to the rebuttal of the rejection over U.S. Patent 5,602,102.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Applicant's arguments that Games discloses the excluded transgene construct is persuasive to over come the rejection under 35 U.S.C. 103(a) as being unpatentable over Games et al (1995) Nature 373, 523-527. Further Games does not provide teaching, suggestion and

motivation for methods of assay using mice comprising transgene constructs within the scope of the claims.

Claims 1-7,9,11,13,15-20,22,23,26,29-34,36,38,40,42-50,53,54,57 and 58 remain rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,811,633 for reasons of record as set forth in papers no. 5, mailed April 27, 2000 and no. 11, mailed January 29, 2001.

'633 teaches a transgenic mice whose genome comprises and expresses a variety of APP transgene constructs: cDNA encoding APP770, APP751, APP695 and FAD mutants of these cDNA's and a cDNA genomic construct, a specific version of which is claimed (col. 7, line 65 to col. 8, line 8, line 32 to col. 9, line 8 and claims 1 and 3-6). The construct is disclosed and claimed to be operatively linked to a promoter, and such as the PDGF promoter (col. 9, lines 43-48 and claims 1 and 6). The mice are taught to be an assay model for determining compounds for the treatment of Alzheimer's Disease (col. 15, lines 31-40).

Applicant argues that they have excluded the construct of the exemplary mouse. This argument is not persuasive.

The amendment only excludes a particular cDNA/genomic APP construct comprising an APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6,7, and 8, and exons 7 and 8. '633, however, teaches the use of any APP cDNA/genomic hybrid construct ('633, col. 5, lines 21-25). Thus, '633 teaches the assays using mice comprising transgene constructs within the scope of the claims. In particular see present claim 3. Thus, while applicant has excluded one disclosed, and claimed, APP cDNA/genomic DNA construct, '633 teaches non-excluded APP cDNA/genomic DNA construct.

Claims 1,2,5-7,9,11,13,15-20,24-26,28-30,33,34,36,38,40,42-48,51-53 and 56 remain rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,612,486 for reasons of record as set forth in papers no. 5, mailed April 27, 2000 and no. 11, mailed January 29, 2001.

'486 teaches a transgenic mouse whose genome comprises a transgene comprising APP695 K595M, N596L, the Swedish mutation operably linked to the NSE promoter (col. 13, line 56-66; col. 24, lines 45-53 and col. 20, lines 16-20, and claims 1-16). These mutations are identical to K670M, N671L. The variation in numbering is due to '486 referring to the APP695 numbering and the instant claims to the APP770 numbering. APP695 K670M, N671L is specifically claimed. The mice of '486 are taught to be useful in screening assays to determine pharmaceuticals for treating Alzheimer's Disease (col. 23, lines 44-50).The specification clearly defines the NSE promoter as one promoter to be used in the instant claims.

Applicant argues that whether an artisan would in fact achieve a transgenic mouse from the teachings of the '486 patent would depend on subjective factors, probabilities and unknowns. Applicant also argues that the examiner has not provided a secondary reference or common knowledge in the at that the presently claimed transgenic animals might be obvious. These arguments are not persuasive.

Applicant is referred to the rebuttal offered above to WO 95/11968. Applicant has not provided any evidence that the mice of '486 will not exhibit the claimed expression levels. The probability that applicant argues is that the artisan may not know the phenotype because the artisan may not assay a sufficient number of mice, or may use the wrong assay criteria. This does not rise to the level that the mice will not have the phenotype. A phenotype is not required to be recognized or known to be inherent. If the structure of the transgene of the transgenic mice is

the same, or is an embodiment of applicant's claim it will be expressed to the recited expression level. Why wouldn't it? Copy number isn't the answer. The mice in '968 did express the APP transgene. Why wouldn't the mice of '486 if assayed under applicant's conditions express at this level? There is no possibility that the transgene won't be so expressed. Applicant's claims states that the transgene is expressed to a particular level. Applicant needs to supply evidence that the mice of '486 do not show the phenotype. Thus, the it is maintained that the phenotype is inherent.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20,22-26,29-555,57 and 58 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for testing or screening compounds for an effect on an Alzheimer's disease marker wherein a compound of interest is administered to transgenic mice whose somatic and germ cells contain a nucleic acid construct comprising a PDGFβ promoter operatively linked to a cDNA-genomic DNA hybrid sequence, wherein said hybrid sequence contains a cDNA sequence encoding APP770 with a mutation of valine for phenylalanine at position 717, wherein a genomic APP DNA sequence consisting of exon 6 and an amount of the adjacent downstream intron sufficient for splicing, the KI and OX-2 coding region and an amount of each of their upstream and downstream introns sufficient for splicing, and exon 9 and an amount of the adjacent upstream intron sufficient for splicing is substituted into the corresponding region of the cDNA sequence encoding APP770 with a mutation of valine for phenylalanine at position 717, wherein expression of the transgene results

in the claimed phenotype at 2-4 months of age, and where the Alzheimer disease marker is an increase or decrease in a protein selected from the group consisting of synaptophysin, GFAP, phosphorylated tau, phosphorylated neurofilaments, MAP-2, Aβtot, Aβ1-42, Aβ1-40, FLAPP + APPα and APPβ; where the Alzheimer's disease marker is a behavior selected from the group consisting of working or reference behavior, locomotor activity, emotional reactivity and object recognition; and where the Alzheimer's disease marker is a histopathology selected from the group consisting of compact plaques, neuritic dystrophy, gliosis, Aβ deposits, decreased synaptic density and neutrophil abnormalities, does not reasonably provide enablement for the nucleic acid constructs specifically claimed and the breadth of mammals for reasons of record as set forth in papers no. 5, mailed April 27, 2000 and no. 11, mailed January 29, 2001. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant argues that there is a crucial distinction between anticipation/obviousness and enablement. Applicant argues that the enablement is determined from the specification and the prior art, and anticipation/obviousness is determined from the prior art alone. Applicant argues that while the prior art may be tempting to follow, the artisan might be uncertain as to how many animals to screen and the phenotypes to screen for. However, applicant argues that an artisan reading the specification has the benefit knowing what to screen for and knowledge that such animals can be achieved. This argument is not persuasive.

While it is understood that applicant is trying to defend his arguments regarding the anticipation and obviousness rejections of record in this and previous office actions, the essential factor is that inherency doesn't require that the phenotype under debate ever be realized. If the

structure is the same, then the phenotype or characteristic sought is inherent. Further the relevant prior art or art at the time of filing can support a lack of enablement.

Applicant has miss-characterized the examiner's comments regarding *In re Wands.* The examiner fully believes that the Wands factors for enablement are relevant to this and every enablement rejection. In fact the enablement rejection has been constructed with the Wands factors in mind. The issue at hand is whether or not the unpredictable nature of transgenic animal production weighs in against applicant's claims. The examiner would agree that unpredictability in transgenesis arises from the fact that random factors affect sites of integration and copy number of the transgene within the genome. The examiner agrees that the level of experimentation is high and that the level of skill in the art is also high. However, it is the teachings in the art and the guidance in the specification that have led to the above scope rejection. Applicant has overcome this unpredictability with one transgenic construct, the one to which a scope rejection has been given.

Applicant argues that Lannfelt indicates that previous workers in the field have failed in generating transgenic animals with characteristics of Alzheimer's Disease due to difficulty in obtaining a high level of APP transgene expression. Applicant argues that Lannfelt notes that expression levels of the APP transgene were low. Lannfelt does not say that achieving high expression of the APP transgene would have been difficult if that was one's goal. Moreover, applicant argues, the claims specify a specific level of Aβ expression not disclosed in Lannfelt. These arguments are not persuasive.

Lannfelt teaches that the problem achieving mouse models of Alzheimer's Disease was because the mice so far only expressed low levels of amyloid protein, Aβ. Applicant in their specification discloses the production of a mouse that achieves sufficient levels of Aβ production

that the mouse develops some characteristics of Alzheimer's Disease. For this mouse a scope has been given above. In other words, Lannfelt stated an art recognized problem, and applicant has found one means to overcome the problem.

Applicant states that they agree with the examiner that the behavioral tests would not be applicable to cells, but they did not amend the claims accordingly. It is unclear to the examiner why applicant wants a claim that is scientifically inappropriate.

Applicant argues that they have included screening markers in the claims that are suspected of being associated with Alzheimer's Disease. Applicant argues that these markers would be useful to a researcher in determining the affect of agents in transgenic animals with Alzheimer's disease characteristics. Applicant argues that although the agents may not indicate an agent that has an affect on Alzheimer's disease, the experiment would indicate that the agent exerts a pharmacological activity that differs between transgenic animals Alzheimer's pathology and control animals. This argument is not persuasive.

The use disclosed for the animals is stated on page 10, lines 16-17 of the specification: the construction of transgenic animal models for testing potential treatment for Alzheimer's Disease is described. There is no disclosure for determining agents that have different effect(s) on the claimed indica in the transgenic mice claimed and control mice. Applicant is asserting an non-disclosed use for the animals post-filing. This is not permissible.

Claims 8,10,12,14,35,37,39 and 41 are free of the prior art. At the time of filing the cited prior art did not teach or suggest a method for testing compounds for an effect on an Alzheimer's Disease maker using a transgenic mouse and testing the markers claimed. The art at the time of

filing did not teach the association of the markers claimed in 8,10,12,14,35,37,39 and 41 as being associated with Alzheimer's disease.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126. The examiner's SPE is Deborah Reynolds, whose telephone number is (703) 305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Art Unit Patent Analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

The fax number is (703) 308-4242.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1630

Dr. D. Crouch
March 8, 2002